Remarks for Senate Subcommittee Hearing
Paul S. Aisen, MD
Professor, Departments of Neurology and Medicine
Director, Memory Disorders Program, Georgetown University Medical Center
Acting Director, Alzheimer's Disease Cooperative Study
May 15, 2007

Alzheimer's disease is among the world's most important health care problem. It is a disease of aging, and as the U.S. population gets older, this problem grows: we have over 5 million cases today, and may reach 15 million by 2050. Effective prevention and treatment are essential.

Useful treatments for the cognitive symptoms of AD have only been available since 1993. Today's treatments represent a significant advance, built on basic and clinical studies conducted by NIH-funded investigators, then followed through by the pharmaceutical industry. This pattern continues: academic investigators have made tremendous advances in recent years, and have worked with industry to move us close to breakthrough disease-modifying treatment.

Most important among these advances is identification of the specific molecular cause of AD: the amyloid peptide. This peptide is the principal component of the amyloid plaque, one of the hallmark lesions in the Alzheimer's disease brain. How do we know that this peptide is the pivotal molecule? Because every known genetic cause of the disease directly influences the generation of the amyloid peptide. The only reasonable conclusion is that this peptide drives the disease process.

Therapeutically, this means that we can now realistically expect to slow or halt the disease process. We have a specific, feasible target for therapeutic interventions. We have confidence that treatments that successfully reduce the accumulation of the amyloid peptide in human brain will slow or stop progression of this disease. And coupled with earlier identification of disease (even before the symptoms indicative of the diagnosis are present), we can hope to dramatically reduce the impact of Alzheimer's disease.

We have the tools to develop effective anti-amyloid treatments. We have model systems in our laboratories that allow us to screen and test potential treatments for impact on amyloid accumulation. The result is that numerous promising therapies are reaching the stage of clinical testing.

NIH funding has played an indispensable role in bringing us to this point, and will continue to be pivotal in the final clinical development programs.

The Alzheimer's Disease Cooperative Study (ADCS) is a large research consortium funded by the National Institute on Aging to develop tools and conduct trials to improve the treatment of Alzheimer's disease. The ADCS has been continuously funded since 1991. Accomplishments of this program include:

- establishment and refinement of the most widely used assessment tools for clinical trials in AD
- establishment of diagnostic criteria and study methodology for "Mild Cognitive Impairment," the Alzheimer's prodromal syndrome
- demonstration of the effectiveness of antioxidant therapy for AD treatment
- demonstration of lack of effectiveness of widely used treatments including anti-inflammatory drugs and estrogen
- demonstration of the only treatment effective in the management of Mild Cognitive Impairment
- the ADCS provides the infrastructure for the Alzheimer's Disease Neuroimaging Initiative, a landmark collaboration between the pharmaceutical industry and NIH to establish the best biomarkers of the disease, to better enable the development of disease-modifying treatments

The work of the ADCS has been pivotal in nearly every major Alzheimer's trial conducted by the academic community and the pharmaceutical industry.

The ADCS is currently conducting clinical studies of promising new treatments for Alzheimer's disease. The ADCS is particularly focused on the evaluation of treatments currently used for other indications, or not otherwise being pursued by the pharmaceutical industry as therapy for AD.

For example:

Statins are among the most widely prescribed drugs in the world. Laboratory studies have shown that cholesterol and statin drugs have an important influence on the accumulation of the amyloid peptide. The ADCS is now completing a definitive trial of a readily available statin (simvastatin) to determine whether it can slow the progression of AD.

DHA (docosahexaenoic acid) is an omega-3 fatty acid present in algae and fish. DHA plays a critical role in the function of brain cells, and levels are depleted in the brains of individuals with Alzheimer's disease. Oral supplements with DHA are effective in restoring brain levels, and, for reasons incompletely understood, DHA markedly reduces amyloid accumulation in brain. The ADCS has just launched a large multicenter study to determine the impact of DHA supplementation on the rate of progression of AD.

One very exciting approach to reducing amyloid accumulation involves the use of antibodies directed against the amyloid peptide. A number of pharmaceutical companies are conducting active and passive amyloid immunotherapy programs, using either vaccinations derived from amyloid or manufactured antibodies to reduce amyloid levels in brain. IVIg is pooled human immunoglobulin, essentially human antibodies derived from donated blood; it is a standard treatment for certain immune and inflammatory diseases. IVIg has been found to contain substantial amounts of naturally occurring anti-amyloid antibodies, and preliminary studies suggest that infusions of IVIg result in

stabilization or improvement of AD. The ADCS is preparing to launch the first definitive study of the safety and effectiveness of IVIg infusions to treat AD.

Huperzine A is a natural extract of a Chinese herb. The purified compound is a highly effective and well tolerated cognitive enhancer, and may be superior to currently available symptomatic treatments for AD. In addition, laboratory studies show that huperzine A protects brain cells against amyloid. The ADCS is currently completing the first controlled study of huperzine A conducted outside China.

As we move closer to effective disease-modifying treatments for Alzheimer's, we are looking toward the testing of preventive measures. But to assess the impact of a preventive treatment, a large number of healthy older individuals must be studied for a number of years. We do not yet have workable tools to allow the efficient conduct of such studies. The ADCS is now conducting a study of Home-Based Assessments, cognitive assessment procedures utilizing computers, interactive phone systems and mail-in tools, to develop the most efficient methods for the conduct of prevention studies without requiring participants to leave their homes.

This is an incredibly exciting time in the field of Alzheimer's disease therapeutic research. We are close enough to be confident of success in the development of breakthrough therapies. How fast we get there, whether it will take a few years or fifteen, depends on the resources brought to bear. With academic-industry cooperation, and adequate funding from both, progress will be rapid.

There are potential breakthrough studies waiting for funding now. For example, a collaboration between NIH and Israeli scientists has led to the discovery of a compound called NAP. NAP is a fragment of a natural brain protein. In the lab, NAP is the most potent neuroprotective compound ever discovered; it can rescue brain cells from many toxins, including the amyloid peptide. Recently completed lab studies show a remarkable effect of NAP on the pathological cascade of Alzheimer's disease. Human studies of NAP have been initiated, but a definitive trial in AD requires NIH funding; an application is currently in review.

Funding priorities should be determined not only by the magnitude of the problem being addressed, but by the likelihood that investment will yield important results. At this point in time, no investment carries more promise than funding for Alzheimer's disease therapeutic research.